RESEARCH ARTICLE

Precentral degeneration and cerebellar compensation in amyotrophic lateral sclerosis: A multimodal MRI analysis

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Abstract

Amyotrophic lateral sclerosis (ALS) is a progressive and intractable neurodegenerative disease of human motor system characterized by progressive muscular weakness and atrophy. A considerable body of research has demonstrated significant structural and functional abnormalities of the primary motor cortex in patients with ALS. In contrast, much less attention has been paid to the abnormalities of cerebellum in this disease. Using multimodal magnetic resonance imaging data of 60 patients with ALS and 60 healthy controls, we examined changes in gray matter volume (GMV), white matter (WM) fractional anisotropy (FA), and functional connectivity (FC) in patients with ALS. Compared with healthy controls, patients with ALS showed decreased GMV in the left precentral gyrus and increased GMV in bilateral cerebellum, decreased FA in the left corticospinal tract and body of corpus callosum, and decreased FC in multiple brain regions, involving bilateral postcentral gyrus, precentral gyrus and cerebellum anterior lobe, among others. Meanwhile, we found significant intermodal correlations among GMV of left precentral gyrus, FA of altered WM tracts, and FC of left precentral gyrus, and that WM microstructural alterations seem to play important roles in mediating the relationship between GMV and FC of the precentral gyrus, as well as the relationship between GMVs of the precentral gyrus and cerebellum. These findings provided evidence for the precentral degeneration and cerebellar compensation in ALS, and the involvement of WM alterations in mediating the relationship between pathologies of the primary motor cortex and cerebellum, which may contribute to a better understanding of the pathophysiology of ALS.

KEYWORDS

amyotrophic lateral sclerosis, cerebellum, fractional anisotropy, functional connectivity, gray matter volume

1 | INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive and intractable neurodegenerative disease characterized pathologically by the degeneration

and loss of both upper motor neurons of the corticospinal tract, and lower motor neurons of the brainstem and spinal cord anterior horns (Turner, 2011). Although it has been more than 100 years since Jean-Martin Charcot first described ALS (Kumar, Aslinia, Yale, & Mazza, 2011),

the potential pathogenesis of ALS remains elusive. Of note, however, several hypotheses have been proposed regarding the mechanisms underlying the neurodegeneration in ALS. In particular, the excitotoxicity hypothesis, which proposes that neurodegeneration in ALS is associated with selective neuronal deaths that occur as a result of overstimulation of the glutamate receptors in the brain (Bakulin, Chervyakov, Suponeva, Zakharova, & Piradov, 2016; Van Den Bosch, Van Damme, Bogaert, & Robberecht, 2006), has promoted the development of riluzole, the only drug licensed for treating ALS. Unfortunately, riluzole could only prolong survival by 2–3 months and provide no cure for ALS (Bensimon, Lacomblez, Meininger, & Group, 1994; Miller, Mitchell, Lyon, & Moore, 2007).

In recent years, advances in neuroimaging techniques have made it possible to precisely and noninvasively explore the macroscopic changes in human brain *in vivo*. Using these techniques, a considerable number of studies have documented aberrant brain structure and function in patients with ALS, which have provided valuable insights into the pathophysiology and degenerative process of this disorder. Notably, alterations in the structure and function of the primary motor cortex are among the most consistently reported findings. For example, voxel-based morphometry (VBM) studies have revealed gray matter volume (GMV) decreases in the motor cortex of patients with ALS (Agosta et al., 2007; Grosskreutz et al., 2006; Kassubek et al., 2005), while surface-based morphometry studies have discovered lower cortical thickness of the primary motor cortex in ALS compared to healthy controls (Agosta et al., 2012; Libon et al., 2012; Roccatagliata, Bonzano, Mancardi, Canepa, & Caponnetto, 2009). Using diffusion tensor imaging (DTI), studies have consistently demonstrated decreased fractional anisotropy (FA) and increased mean diffusivity in the corticospinal tract of patients with ALS (Canu et al., 2011; Ding et al., 2011; Keil et al., 2012). Meanwhile, some resting-state functional magnetic resonance imaging (fMRI) studies showed reduced FC in the sensorimotor network (especially the primary motor cortex) (Jelsoe-Swain et al., 2010; Tedeschi et al., 2012) while several task-based fMRI studies reported enhanced hemispheric activation of the premotor areas and primary motor cortex in patients with ALS (Cosottini et al., 2012; Kollewé et al., 2011; Konrad et al., 2002; Poujois et al., 2013). This body of evidence suggests that changes in the primary motor cortex play important roles in the pathogenesis of ALS.

In contrast to the aforementioned abnormalities in the primary motor cortex, much less attention has been paid to the cerebellar abnormalities in patients with ALS. In fact, being part of the extrapyramidal system, the cerebellum is reciprocally connected with various cortical brain regions (Middleton & Strick, 2000), and has long been considered as crucial for intact motor control and coordination (Tan et al., 2014). In previous neuroimaging studies, structural and functional abnormalities of the cerebellum have been reported in patients with ALS. For example, some VBM studies found significantly decreased GMV in the cerebellum in patients with ALS (Gellersen et al., 2017; Tan et al., 2014; Thivard et al., 2007). Using DTI, studies reported decreased FA in multiple regions of the cerebellum in patients with ALS (Bede et al., 2015; Keil et al., 2012). Meanwhile, both decreased and increased functional connectivity (FC) have been reported for some subregions of cerebellum in patients with ALS (Agosta et al., 2011; Menke et al., 2016; Zhou et al., 2013). However, most of these studies were performed using one single imaging modality.

To our knowledge, few multimodal studies combining the three MRI modalities has been conducted in a large patient cohort to fully characterize the cerebellar abnormalities, as well as the role played by these abnormalities in the pathophysiology of ALS.

Therefore, to explore the relationship between alterations in precentral gyri and cerebellum as well as possible mechanism underlying this relationship in a large cohort, we performed a multimodal MRI study to characterize the structural and functional brain alterations in patients with ALS ($N = 60$) as compared with demographically matched healthy controls ($N = 60$). First, a whole-brain VBM analysis was conducted to examine the gray matter (GM) alterations in patients with ALS compared with healthy controls. Second, a voxel-wise contrast of FA was conducted between the two groups to examine the integrity of the white matter (WM) tracts that are connected to brain regions associated with GM alterations. Third, seed and region of interest (ROI) based FC analyses were conducted to investigate the functional correlates of the structural alterations in patients with ALS compared with healthy controls. Finally, intermodal correlation and exploratory mediation analyses were conducted to investigate the interrelationships among multimodal imaging features as well as the mechanism underlying such relationships.

2 | METHODS

2.1 | Subjects

Sixty patients with ALS (21 women, 39 men, mean age = 48.77, range = 26–69 years) and demographically matched healthy controls (21 women, 39 men, mean age = 48.15, range = 24–70 years) were included in this study. In brief, patients were recruited from the Medical Research Ethics Committee of the Southwest Hospital and were diagnosed with sporadic probable or definite ALS according to the El Escorial criteria (Brooks, Miller, Swash, & Munsat, 2000). All patients were measured to assess the functional status using the revised ALS Functional Rating Scale (ALSFRS-R) (maximum score is 48, with a lower score indicating greater motor impairment) (Cedarbaum et al., 1999). Disease duration, reflecting the temporal extent from the symptom onset to the scanning date (months) and rate of disease progression, defined as $(48 - \text{ALSFRS-R}) / (\text{disease duration})$, were also obtained on the day of scanning.

In this study, to be included, patients had to have: the ability to lie supine in the scanner for up to 40 min; no family history of motor system diseases; and without any specific treatment before. Patients would be excluded if they had: clinical diagnosis of frontotemporal dementia (Brooks et al., 2000); cognitive impairment (Montreal Cognitive Assessment score <26) (Nasreddine et al., 2005); and other neurological and medical diseases. Healthy controls matched for gender and age were recruited from the local community. None of the healthy controls were related to the patients with ALS. All participants were right handed based on measurements of the Edinburgh inventory. The detailed demographic and clinical characteristics of all participants are presented in Table 1. Written informed consent in accordance with the medical ethics approval of the research project was also provided by all participants.

2.2 | MRI acquisition

All MR data were acquired on a Siemens 3T Tim Trio scanner using an eight-channel head coil. The neuroimaging protocol included T1-weighted, diffusion-weighted and resting-state fMRI. Briefly, T1-weighted images were acquired using a three-dimensional magnetization-prepared rapid gradient-echo imaging sequence with repetition time (TR) = 1900 ms, echo time (TE) = 2.52 ms, inversion time = 900 ms, flip angle = 9°, matrix = 256 × 256, thickness = 1.0 mm, gap = 0 mm, 176 slices, and voxel size = 1 × 1 × 1 mm³. Whole-brain DTI images were acquired using a single-shot twice-refocused spin echo sequence with TR = 10,000 ms, TE = 92 ms, 64 diffusion directions ($b = 0$ and 1,000 s/mm²), matrix = 128 × 124, field of view (FOV) = 256 × 248 mm², and 75 axial slices (thickness = 2 mm, gap = 0 mm). Each participant was scanned twice with the DTI for increased signal-to-noise ratio. Resting-state fMRI images were acquired using an echo planar imaging sequence with 36 axial slices, slice thickness = 3 mm, gap = 1 mm, TR = 2000 ms, TE = 30 ms, FA = 90°, FOV = 192 × 192 mm², matrix = 64 × 64, voxel size = 3 × 3 × 3 mm³, and total volumes = 240. Subjects were instructed to keep their eyes closed, remain still and not to fall asleep for maximum consistency.

3 | MRI DATA ANALYSES

3.1 | VBM analysis

T1-weighted structural images were preprocessed using the Statistical Parametric Mapping 8 (SPM8; <http://www.fil.ion.ucl.ac.uk/spm>) VBM8 toolbox. All structural images were segmented into GM, white matter (WM), and cerebrospinal fluid (CSF). The GM images were normalized to the Montreal Neurological Institute (MNI) space using high-dimensional DARTEL normalization. Images were modulated to ensure that relative GM volumes were well preserved following spatial normalization. Prior to statistical analysis, the normalized modulated GM images were smoothed using a Gaussian kernel with a full width at half maximum (FWHM) of 8 mm.

3.2 | DTI analysis

Diffusion-weighted images were processed using the FMRIB's Software Library (FSL <https://fsl.fmrib.ox.ac.uk/fsl/>). Preprocessing included eddy currents, head motion correction, and brain-tissue extraction (Smith, 2002). The resultant images were then fit with a diffusion tensor model (Jenkinson, Bannister, Brady, & Smith, 2002) to obtain the FA map. Before statistical analysis, the FA maps were normalized to MNI space and smoothed using a Gaussian kernel with FWHM = 8 mm.

To examine whether GMV atrophy were associated with WM microstructural abnormalities, we confined the voxel-wise FA analysis of the two groups within the WM tracts connected to the regions with GMV reductions. To this end, a population-based mask of WM tracts used in subsequent voxel-based analysis was constructed from the WM tracts generated by seed-based probabilistic tractography. Specifically, brain regions with GMV reductions were selected as seed masks for multifiber probabilistic tractography (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007). Fiber tracking was initiated from all voxels of the seed mask to the whole brain to generate 5,000 streamline samples. Voxels with at least one arriving streamline were assigned a value of 1 and 0 otherwise, resulting in a volume of WM tracts in the individual's diffusion space. The volumes of WM tracts were transformed into MNI space and averaged across all participants to obtain a population-based probability map of the WM tracts. Then, a population-based mask of WM tracts was generated by binarizing the population-based probability map with a threshold of $p > 50\%$.

3.3 | Seed-based and ROI-based FC analyses

Preprocessing of resting-state fMRI data were conducted using Data Processing Assistant for Resting-state fMRI Advanced Edition toolbox (<http://rfmri.org/DPARSF>). Main preprocessing steps included removing the first 10 time points, slice timing, head motion correction, realignment, normalizing to MNI space, spatially smoothing using a Gaussian kernel with FWHM = 6 mm, filtering (0.01–0.08 Hz), and removal of nuisance signals containing head motion parameters, WM, and CSF.

TABLE 1 Demographic and clinical data of the participants

	Patients with ALS (N = 60)	Healthy controls (N = 60)	p-Value
Mean age in years (range)	48.77(26–69)	48.15(24–70)	.73
Male/female	39/21	39/21	1.00
Education level in years (range)	12.2 (5–18)	12.7 (6–19)	.48
Limb/bulbar/both onset	47/12/1	–	–
Classic/LMN-D/UMN-D/PLS/PMA	43/7/7/2/1	–	–
MoCA score (range)	27.38(26–30)	27.63(26–30)	.29
Mean disease duration in months (range)	21.05(2–132)	–	–
Mean ALSFRS-R (range)	32.62(16–45)	–	–
Mean disease progression rate (range)	1.36(0.02–6.50)	–	–

Note. The ALS patients were subdivided into five phenotypes: classic, LMN-D, UMN-D, PLS, and PMA.

Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale; MoCA, Montreal Cognitive Assessment; LMN-D, lower motor neuron dominant; PMA, progressive muscular atrophy; PLS, primary lateral sclerosis; UMN-D, upper motor neuron dominant.

To examine whether GMV abnormalities in patients with ALS are associated with changes in brain connectivity, brain region with GMV reductions in the VBM analysis was used as a seed for seed-based voxel-wise FC analysis. FC maps, calculated by assessing the correlation coefficients between the mean time series of mask and that of every voxel over the whole brain, were converted into *z* maps using Fishers' *z* transformation so as to better implement statistical analysis.

Meanwhile, ROI-based FC was also compared between the two groups for brain regions showing significant between-group differences in GMV.

3.4 | Statistical analysis

Voxel-wise contrasts of GMV, FA, and seed-based FC were performed between the two groups using second-level group analysis implemented with SPM8. Specifically, each contrast was entered into a voxel-wise general linear model including diagnosis, age, and gender as covariates. In particular for voxel-wise FA analysis, an explicit mask (the population-based mask generated in DTI analysis) was introduced to confine the analysis to the WM tracts that are connected to the brain regions with GMV reductions. Subsequently, the statistical results were thresholded at voxel-wise $p < .005$ and corrected for multiple comparisons at the cluster level using Gaussian random field theory. The level of significance was set at $p < .05$ after multiple-comparison correction. Group comparison of ROI-based FC controlling gender and age as covariates were performed using SPSS. Additionally, Pearson's correlation coefficient was calculated to examine the relationship between the mean GMV/FA/FC of the surviving clusters in voxel-wise analysis and the ALSFRS-R scores of the patients with ALS.

3.5 | Intermodal correlation and exploratory mediation analyses

Pair-wise correlation analyses were performed among GMV, FA, and FC using SPSS to investigate their interrelationships. Using Sobel test of the "multilevel" package in R, further exploratory mediation analyses were conducted to examine the underlying mechanism of such relationships. Specifically, we explored whether the relationships between GMV within the regions of between-group difference and seed-based or ROI-based FC within the regions of between-group differences were mediated by the FA of the clusters obtained in DTI analysis. We also explored whether WM FA of the clusters obtained in DTI analysis could mediate the relationship between the GMV of the regions with between-group differences.

4 | RESULTS

4.1 | VBM analysis

Compared with healthy controls, we found focal GM atrophy in the left precentral gyrus in patients with ALS (cluster size: 1320 voxels; peak MNI coordinate: $x = -37.5$, $y = -10.5$, $z = 39$; peak *t* value: -4.50) (Figure 1). In addition, patients with ALS also showed increased GMV in the bilateral cerebellar subregions of Crus II, VIIIb, and VIIIa (according

to the probabilistic cerebellar atlas (Diedrichsen, Balsters, Flavell, Cussans, & Ramnani, 2009); cluster size: 1,388 voxels; peak MNI coordinate: $x = -33$, $y = -36$, $z = -46.5$; peak *t* value: 5.03 for the cluster in the left hemisphere, and cluster size: 1,192 voxels; peak MNI coordinate: $x = 37.5$, $y = -46.5$, $z = -54$; peak *t* value: 5.47 for the cluster in the right hemisphere) compared with healthy controls (Figure 1).

4.2 | DTI analysis

Compared with healthy controls, we found two clusters where patients with ALS showed significantly decreased FA (cluster size: 1,373 voxels; peak MNI coordinate: $x = -16$, $y = -22$, $z = 58$; peak *t* value: -5.71 for one cluster, and cluster size: 310 voxels; peak MNI coordinate: $x = -6$, $y = -24$, $z = -32$; peak *t* value: -6.19 for another cluster) (Figure 2). These clusters mainly involved the left corticospinal tract and the body of corpus callosum. In addition, correlation analysis showed a significant positive correlation between the mean FA of these clusters and the ALSFRS-R scores within the patient group ($p = .009$, $r = .344$) (Figure 3).

4.3 | Seed-based and ROI-based FC analyses

Compared with healthy controls, the seed-based FC analysis revealed two clusters where patients with ALS showed significantly decreased FC to the precentral seed region. These two clusters anatomically involved the bilateral postcentral gyrus, precentral gyrus, inferior and superior parietal lobule, and Brodmann area 3 (cluster size: 1,390 voxels; peak MNI coordinate: $x = -3$, $y = -30$, $z = 78$; peak *t* value = 4.57), lingual and fusiform gyrus, and cerebellum anterior lobe (cluster size: 913 voxels; peak MNI coordinate: $x = 36$, $y = -75$, $z = -18$; peak *t* value = 4.38) (Figure 4).

Using the brain regions with altered GM volume as ROIs, the ROI-based FC analysis revealed decreased FC between the precentral ROI and the right cerebellar ROI ($p = .02$).

4.4 | Intermodal correlation and exploratory mediation analyses

Significant positive correlations were found between GMV and FC of the left precentral ROI ($r = .232$, $p < .011$), between FC of the precentral ROI and FA of the altered WM tracts ($r = .283$, $p < .002$), and between GMV of the precentral ROI and FA of the altered WM tracts ($r = .431$, $p < .001$). A significant negative correlation was found between GMVs of the precentral ROI and the cerebellar ROI ($r = -.219$, $p < .017$) (Figure 5).

In addition, we found that FA of the clusters obtained in DTI analysis had a mediating effect on the relationships between GMV of the precentral ROI and FC of the regions with between-group differences in seed-based FC (Sobel statistics = 2.09, $p < .035$) as well as the ROI-based FC analysis (Sobel statistics = 2.12, $p < .033$). The FA of the clusters obtained in DTI analysis was also found to mediate the relationship between GMV of the precentral ROI and that of the cerebellar clusters obtained in VBM analysis (Sobel statistics = -2.15 , $p < .031$) (Figure 6).

FIGURE 1 Brain regions showing significant GMV alterations in patients with ALS compared with healthy controls. The results were corrected for multiple comparisons using Gaussian random field theory. Cold color denotes regions with decreased GMV in patients with ALS compared with healthy controls, while warm color denotes regions with increased GMV in patients with ALS compared with healthy controls. ALS, amyotrophic lateral sclerosis; GMV, gray matter volume [Color figure can be viewed at wileyonlinelibrary.com]

5 | DISCUSSION

In the present study, a multimodal MRI-based analysis was conducted to investigate the structural and functional abnormalities in patients

with ALS compared with healthy controls. The key findings of our study were summarized as follows. First, compared with healthy controls, patients with ALS showed decreased GMV in the left precentral gyrus and increased GMV in the bilateral cerebellar subregions of Crus

FIGURE 2 WM alterations in patients with ALS. The upper pane displayed the three-dimensional rendering of the WM tracts with decreased FA in patients with ALS compared with healthy controls. The lower pane displayed four sliced views (coronal) of the WM tracts with decreased FA in patients with ALS compared with healthy controls. The color bar indicates the t values. The results were corrected for multiple comparisons using Gaussian random field theory. A, anterior; ALS, amyotrophic lateral sclerosis; FC, functional connectivity; FA, fractional anisotropy; L, left; P, posterior; R, right; WM, white matter [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 3 Positive correlation between mean FA of the altered WM tracts and ALSFRS-R in patients with ALS. ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale; FA, fractional anisotropy; WM, white matter [Color figure can be viewed at wileyonlinelibrary.com]

II, VIIb, and VIIIa. Second, patients with ALS showed reduced FA in the left corticospinal tract and the body of corpus callosum, which was shown to be positively correlated with the ALSFRS-R scores. Third, using both seed-based and ROI-based FC analyses, we found significantly decreased FC of the precentral ROI in patients with ALS compared with healthy controls. Fourth, we found significant inter-modal correlations among GMV of the precentral ROI, FA of the altered WM tracts, and FC of the precentral ROI. Further mediation analyses showed that FA of the altered WM tracts could mediate the relationships between GMV and FC of precentral ROI and between GMVs of the precentral ROI and the cerebellar ROI. Taken together,

these findings provide evidence for the precentral degeneration and cerebellar compensation in ALS, and the involvement of WM alterations in mediating the relationship between the pathologies of the primary motor cortex and the cerebellum, which may provide new insights into the pathophysiology of this disease.

5.1 | GM alterations in ALS

Compared with healthy controls, we found significantly decreased GMV in the left precentral gyrus in patients with ALS. This finding is consistent with many previous studies. For example, several independent VBM studies have showed decreased GMV in patients with ALS compared with healthy controls (Agosta et al., 2007; Grosskreutz et al., 2006; Kassubek et al., 2005). Meanwhile, some surface-based morphometry studies have reported significant reductions in cortical thickness and cortical surface area in the precentral gyrus in patients with ALS (Agosta et al., 2012; Libon et al., 2012; Roccatagliata et al., 2009). More importantly, postmortem studies have demonstrated the absence of Betz cells (accounting for approximately 5% of the total pyramidal cells in the precentral gyrus) from Layer 5 of the precentral gyrus in patients with ALS and that the remaining pyramidal cells were significantly smaller than those seen in healthy controls (Eisen & Weber, 2001). Collectively, the present result, together with those of previous studies, suggests that structural abnormality in the precentral gyrus might be a common finding in patients with ALS. In fact, the primary motor cortex, as a major source of descending motor commands for voluntary movement (Lemon, 2008), has been involved in various motor functions, such as contralateral limb movement, contralateral face/mouth movement, and swallowing/laryngeal movement (Kakei, Hoffman, & Strick, 1999; Rathelot & Strick, 2009), and so forth. Of note, it has been shown that focal GM atrophy in the precentral gyrus

FIGURE 4 Brain regions showing decreased FC to the precentral ROI in patients with ALS compared with healthy controls. The color bar indicates the *t* values. The results were corrected for multiple comparisons using Gaussian random field theory. ALS, amyotrophic lateral sclerosis; FC, functional connectivity [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 5 Correlations among GMV, FA, and FC using data of both groups. (a) Positive correlation between GMV of the precentral ROI and ROI-based FC. (b) Positive correlation between FA of the altered WM tracts and ROI-based FC. (c) Positive correlation between GMV of the precentral ROI and FA of the altered WM tracts. (d) Negative correlation between GMVs of the precentral ROI and cerebellar ROI. ALS, amyotrophic lateral sclerosis; FC, functional connectivity; FA, fractional anisotropy; GMV, gray matter volume; WM, white matter [Color figure can be viewed at wileyonlinelibrary.com]

is linearly associated with functional disabilities of particular body regions in ALS (Bede et al., 2013). Presumably, the decreased GMV in the precentral gyrus may be the anatomical substrate underlying the functional deficits in patients with ALS.

As patients with ALS have been shown to be associated with increased glutamate and decreased GABA in the primary motor cortex (Foerster et al., 2012; Foerster et al., 2013; Pioro, Majors, Mitsumoto, Nelson, & Ng, 1999), it is therefore speculated that the imbalance

FIGURE 6 Mediation path diagrams for FA of the WM tracts using data of both groups. (a) This mediation model illustrates the direct effect of the GMV of precentral ROI on the FA of WM tracts (Path a), the direct effect of the FA of WM tracts on the FC of precentral ROI (Path b), the direct effect of the GMV and FC of the precentral ROI (Path c'), and the mediating (indirect) effect of FA of WM tracts on the relationship between GMV and FC of the precentral ROI. (b) This mediation model illustrates the direct effect of the GMV of precentral ROI on the FA of WM tracts (Path a), the direct effect of the FA of WM tracts on the GMV of cerebellar ROI (Path b), the direct effect of the GMVs of precentral ROI and cerebellar ROI (Path c'), and the mediating (indirect) effect of FA of WM tracts on the relationship between GMVs of the precentral ROI and cerebellar ROI. As indicated by the regression coefficients and *p* values, there were significant mediating effects of WM microstructure alterations on the association between GMV and FC of the precentral ROI or between GMVs of the precentral ROI and cerebellar ROI. FC, functional connectivity; FA, fractional anisotropy; GMV, gray matter volume; WM, white matter [Color figure can be viewed at wileyonlinelibrary.com]

between excitatory and inhibitory signaling contributed to the neuronal damage or loss in the primary motor cortex (Foerster et al., 2012; Foerster et al., 2013), which in turn resulted in reduced GMV in this region in patients with ALS.

Compared with healthy controls, the present study also showed significantly increased GMV in bilateral Crus II, VIIb, and VIIIa of the cerebellum in patients with ALS. This finding is supported by previous PET studies showing higher glucose consumption in the cerebellum in patients with ALS compared with healthy controls (Cistaro et al., 2014; Pagani et al., 2014). Notably, some previous VBM studies have reported decreased GMV in the cerebellum which seems to contradict our current finding (Gellersen et al., 2017; Tan et al., 2014). The underlying mechanism for such discrepancies, however, remains unknown. One possible explanation is that the patient groups of different studies might reside in different disease stages (Braak et al., 2013), which manifested as different endophenotypic alterations in the brain. In this study, the observed GMV increases in bilateral cerebellum may represent adaptive changes to compensate for the GM atrophy of the precentral gyrus (albeit in a futile way) and might exhaust (manifesting as GMV decrease in the cerebellum) as the disease progresses.

5.2 | WM alterations in ALS

Compared with healthy controls, the present study showed significantly decreased FA along the left corticospinal tract as well as the body of corpus callosum in patients with ALS. The involvement of corticospinal tract and corpus callosum abnormalities in ALS has been reported by many previous studies (Filippini et al., 2010; Ince et al., 2003; Zhang et al., 2011). In particular, FA decreases within the corticospinal tract have been recognized as the pathologic hallmark feature in patients with ALS (Borsodi et al., 2017). Indeed, the corticospinal tract is the most important WM tract involved in movement execution of distal extremities (Seo & Jang, 2013), and abnormalities of the corticospinal tract might contribute to the clinical presentations of patients with ALS, such as foot drop, difficulty walking and loss of hand dexterity (Gordon, 2013), and so forth. This speculation was further supported by our result of a positive correlation between mean FA of the significant clusters and ALSFRS-R scores in the patient group. On the other hand, the corpus callosum, as the largest WM structure interconnecting the two cerebral hemispheres (Li, Wu, Liang, & Huang, 2015), is thought to play an important role in interhemispheric communication. Therefore, the observed FA decrease in the corpus callosum may suggest altered interhemispheric information transfer in patients with ALS as evidenced by recent reports of impaired interhemispheric structural and FC (Zhang et al., 2017).

FA measures the movement of water molecules within tissues and was interpreted to reflect the integrity of WM microstructure in brain (Agosta et al., 2010; Basser & Pierpaoli, 2011). In previous neuroimaging studies, alterations in FA have been considered to be associated with various WM pathologic features, such as ischemia, myelination, axonal damage, inflammation, edema (Pfefferbaum et al., 2000; Toosy et al., 2003; T. Zhou et al., 2017), and so forth. Indeed, WM neuropathological changes, including demyelination and axonal damage,

have been documented in previous studies and may account for the decreased FA in the corticospinal tract and corpus callosum in patients with ALS (Alexander, Lee, Lazar, & Field, 2007).

5.3 | FC alterations in ALS

Compared with healthy controls, our seed-based FC analysis revealed decreased FC of the left precentral ROI to multiple brain regions in patients with ALS, involving the bilateral postcentral gyrus, precentral gyrus and Brodmann area 3, and the bilateral fusiform gyrus and cerebellum anterior lobe. Likewise, the ROI-based FC analysis also showed a lower FC between the precentral ROI and the right cerebellar ROI in patients with ALS. These results were consistent with previous studies reporting decreased interhemispheric FC of the primary motor cortex (Fang et al., 2016; Zhang et al., 2017), and were supported by the findings of decreased degree centrality and FC density in the primary motor cortex in patients with ALS (Li et al., 2018; Zhou et al., 2016). Notably, however, there also existed some fMRI studies showing increased FC or activation of the primary motor cortex in patients with ALS (Chiò et al., 2014; Menke et al., 2016). The mixed picture of FC decrease and increase in the primary motor cortex of ALS may reflect a dynamic pathological process mediated by the development of cortical hyperexcitability (Bakulin et al., 2016). Indeed, cortical hyperexcitability is not a static phenomenon but rather shows a pattern of spatiotemporal progression, and may play different roles at different stages of ALS (Bae, Simon, Menon, Vucic, & Kiernan, 2013). Specifically, cortical hyperexcitability could develop via the compensatory mechanism (probably by increasing the FC or activation of the motor cortex) in response to impaired synaptic connections or loss of motor neurons in early stages of ALS; however, the existing resources may not be able to afford an effective compensation in more advanced stages wherein cortical hyperexcitability may start to exert a deleterious effect (showing FC decrease of the motor cortex) in patients with ALS.

5.4 | Intermodal correlation and exploratory mediation analyses

Our findings of intermodal correlation analyses suggest that the abnormalities revealed by GMV, FA, and FC in patients with ALS may not be mutually independent and possibly be mediated by a common pathological process. The result of a positive correlation between the GMV of the left precentral ROI and FC of the affected regions is consistent with previous studies in healthy subjects (Segall et al., 2012), and indicates that decline in GMV can be translated to decline in FC in patients with ALS as a result of the fact that neuronal damage or losses in the precentral gyrus may significantly compromise its neural activity. The result of a positive correlation between FC of the precentral ROI and FA of the altered WM tracts suggests that the functional and structural connection between two brain areas are tightly coupled. Given that brain functions are generally considered to be shaped and constrained by the underlying anatomy (Hermundstad et al., 2013; Honey, Thivierge, & Sporns, 2010), it is tempting to speculate that WM microstructural abnormalities evidenced by FA

reductions may also contribute to the decreased FC in patients with ALS. Moreover, we also found that GMV of the precentral ROI is positively correlated with the FA of the altered WM tracts. This finding may indicate that neuronal death in the primary motor cortex resulted in secondary Wallerian degeneration in adjacent WM tracts (Jang et al., 2017), which in turn led to lower FA in patients with ALS. In addition, we revealed a negative correlation between the GMVs of the precentral ROI and the cerebellar ROI, which might be related to the neurotrophic effect mediated by the underlying WM connections (Cauda et al., 2014).

Several exploratory mediation analyses were performed to explore the underlying mechanisms of interrelationships among GMV, FA, and FC. We found that the relationship between GMV and FC of the precentral ROI is mediated by the FA of the altered WM tracts. This finding may indicate that GMV abnormalities of the precentral gyrus can have an effect on its FC through an indirect pathway of altered WM tracts. In addition, we found that the association between GMVs of the precentral ROI and the cerebellar ROI was mediated by the FA of the altered WM tracts. This result may reflect that neurotrophic effect owing to shared WM tracts plays an important role in mediating the GMVs of the precentral ROI and cerebellar ROI, and that the cerebellum may increase its GMV adaptively in compensation for the disrupted WM tracts so as to maintain normal motor functions. These findings highlight the involvement of WM microstructural alterations in the pathogenesis of ALS and were supported by a previous hypothesis proposing that WM fiber tracts play a crucial role in the propagation of ALS-related pathological processes (Braak et al., 2013).

5.5 | Limitations

Some limitations should be addressed for this study. First, the present study was conducted with a cross-sectional design, which does not allow us to characterize the dynamic development of structural and functional abnormalities in ALS. Future longitudinal studies are warranted to unveil the dynamic pattern of these alterations as the disease progresses. Second, although we recruited a relatively large sample of patients with ALS, the numbers were necessarily lower when patients were divided into subgroups, for example, bulbar versus limb or upper motor neuron versus lower motor neuron predominant. Studies with a larger sample and a more balanced subtype composition are needed to examine whether the structural and functional alterations found in this study were common among different subgroups or driven by pathological processes unique to one particular subgroup.

6 | CONCLUSIONS

In the present study, we demonstrated significant alterations in GMV, WM microstructure, and FC in patients with ALS compared with healthy controls, and that microstructural alterations of relevant WM tracts seem to play important roles in mediating the relationship between the GMV and FC of the precentral gyrus, as well as the relationship between the

GMVs of the precentral gyrus and the cerebellum. These findings provide new insights into the pathophysiology of ALS.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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